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Reduced Brain Potentials to Novelty in Depression: Characterization of Neural Sources by Principal Components Analysis (PCA) of Current Source Density (CSD) Waveforms

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http://psychophysiology.cpmc.columbia.edu/mmedia/sobp2008/novelty.pdf

Abstract

Background: We recently reported reductions in the frontocentral P3 potential to novelty in depression (20 unmedicated patients, 20 healthy controls; 31-channel EEG). This replication and extension was recorded from a high-density montage (67-channels) in a larger, independent sample (49 patients; 49 controls). PCA-CSD methods were used for improved identification and quantification of reference-free components, having sharper topographies that more closely reflect underlying neuronal generators.
Methods: A novelty oddball task (Friedman et al., 1993) included two 300-ms tones (nontargets: 350 Hz, p=.76; targets: 500 Hz, p=.12) and novel sounds (e.g., dog bark, human cough: 100-400 ms, p=.12) in pseudorandom order with 1000 ms ISI using eight 50-trial blocks. Participants responded as quickly as possible to target tones only, with response hand counterbalanced across blocks. Spherical spline CSDs were derived from ERPs, and quantified using unrestricted PCA.
Results: The CSD-PCA solution was consistent with binaural (Kayser and Tenke, 2006) and dichotic (Tenke et al., in press) oddball tasks. However, the P3 source factor (343 ms peak latency), which efficiently summarized medial-parietal target P3b, also included a secondary, midline frontocentral source for novel and target stimuli. Moreover, a preceding factor (241 ms) identified earlier source activity at midcentral sites (Cz maximum) that was specific to novels. This novelty P3 source was preferentially reduced in patients, and confirmed by hemispatial PCA.
Conclusions: Depressed patients show a reduced response to novel distractors, consistent with a deficit in an early attentional response to novelty, and localizable to frontocentral regions within and along the longitudinal fissure.

Introduction

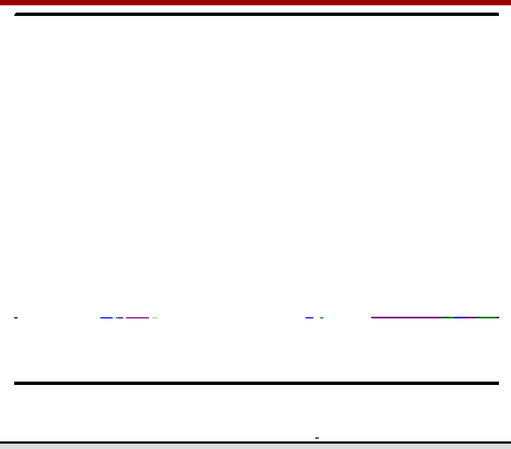
The conflicting reports of reduced P3 amplitude in depressed patients may, in part, be due to the multiple subcomponents comprising the late positive complex, each arising from distinct neural generators and associated with different cognitive processes. We recently reported that depressed patients had reduced novelty P3 compared to healthy controls using a 31-channel montage (Kroppmann, et al., 2006). We report here an independent replication and extension (49 patients; 49 controls) using 67 channels using a higher density montage and reference-free methodology.

Methods

Participants: 49 depressed outpatients (22 male; age = 35.8 ±10.7 yrs; med-free at least 7 days) and 49 healthy adults (23 male; age = 31.0±10.6 yrs; no current or past psychopathology). No neurological disorder, substance abuse, or hearing loss greater than 30 dB in either ear. *Patient Dx*: MDD (*26*), dysthymia (*9*), both (*11*); bipolar (*1*); depression NOS (*2*); comorbid anxiety (*8*); BDI: 13-41 (23.0 + 7.2).
EEG Acquisition and Artifact Procedures: Continuous EEG was recorded using a 72-channel Biosemi ActiveTwo system (256 sps) . Data were rereferenced to nose, bipolar EOG derivations computed, and exported to Neuroscan format using Polyrex (Kayser, 2003) and blink corrected (spatial PCA routine; Neuroscan), Stimulus-locked epochs (1200 ms, 200 ms prestimulus) were extracted. EEG channels containing amplifier drift, residual eye activity, muscle or movement-related artifacts or noise for any given trial were identified using a reference-free approach (Kayser & Tenke, 2006c), and replaced by spherical spline interpolations (Perrin et al 1989) using the data from artifact-free channels if possible (i.e., less than 25% of all channels contain an artifact), as verified by visual inspection. ERP averages were computed for correct targets, nontargets and novels (n>15 for all averages), as well as for Novels in the first and last halves (47 controls, 44 patients, n>8).
CSD – PCA and Hemispatial PCA: Reference-independent CSD waveforms were computed from ERPs using a spherical spline surface Laplacian (Perrin et al, 1989; 50 iterations; m = 4; $\lambda = 10^{-5}$). CSDs were submitted to temporal PCA (covariance matrix, unrestricted Varimax rotation; Kayser & Tenke, 2003, 2006a,b). This approach yields distinctive PCA components (factor loadings waveforms) and corresponding weighting coefficients (factor score topographies), which concisely simplify and quantify the temporal pattern and spatial distribution of underlying neuronal generators. These results were compared to those using a hemispatial PCA (spatial PCA based on hemitopographies, Tenke et al, 2008) to assure that the observed effects are not due to misallocated temporal variance.
Statistical Methods: CSD topographies allow simplified analyses of well-defined regions. Based on *a priori* theoretical grounds and the observed topography of the Novelty P3 source, a repeated measures ANOVA was restricted to four midline sites (Fz, FCz, Cz, CPz; cf Figs. 1-2). Only Novelty effects reported here.

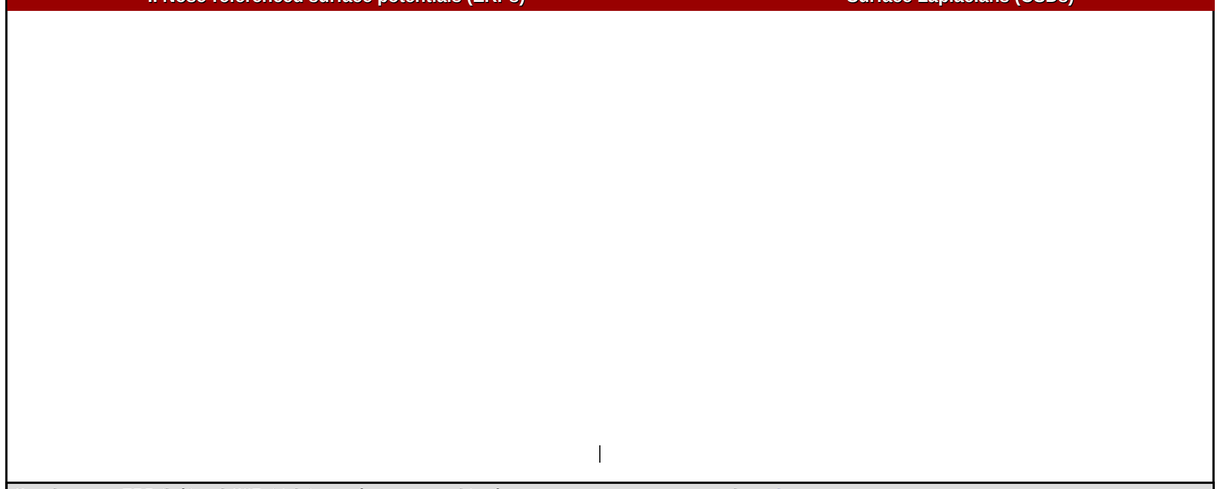
Novelty oddball task: An auditory novelty oddball task (Friedman et al., 1993) was implemented on a Neuroscan STIM system. For each subject, 8 blocks of 50 trials consisting of two 300 ms tones are presented in pseudorandom order (stimulus onset asynchrony = 1000 ms). One nontarget tone of 350 Hz is presented to the subject frequently (p = .76) while the other is an infrequent 500 Hz target tone (p = .12). Novel sounds (i.e., animal sounds, musical instruments, environmental sounds) possessing durations of 100-400 ms are infrequently (p = .12) intermixed with the frequent tones and infrequent target tones. All stimuli are presented binaurally over headphones at 75 db SPL. Subjects are instructed to focus their eyes on a fixation cross displayed on a computer monitor and to respond with a button press as quickly as possible when, and only when, they hear the infrequent target tones. Response hand (right or left) was counterbalanced across blocks.
Task performance: Overall performance was 98.5± 1.9 % correct, but six participants (5 patients) performed at less than 95%. Nontargets: Control= 99.6 ± .6 %; Patient= 99.5 ± .8. Novels: Control= 96.6 ± 4.3; Patient= 96.4 ± 4.2. Targets: Control= 98.7 ± 2.4; Patient= 97.4 ± 4.2 (ns). RT: Control=438 ± 88 ms; Patient=491 ± 87, t= 2.97, df= 96, p= .004).

IIIA. Temporal PCA Solution: Loadings



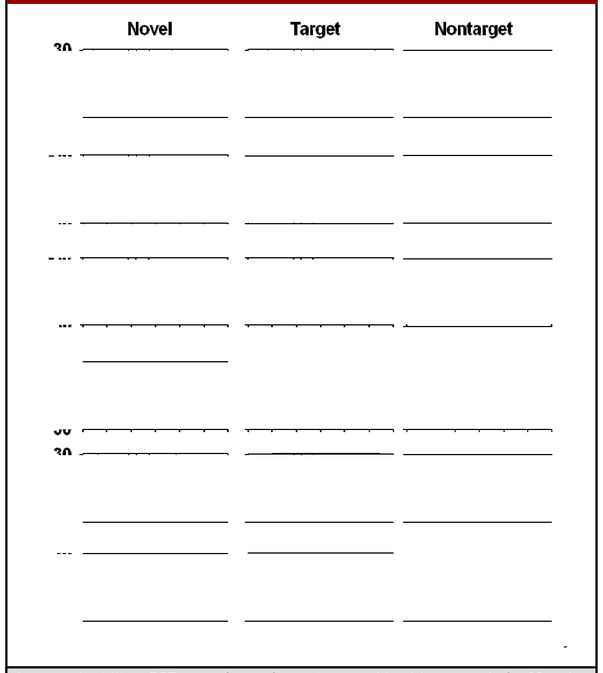
PCA solution: Covariance loading waveforms for first six factors (88.4% total; all >2%).

I. Nose-referenced surface potentials (ERPs) Surface Laplacians (CSDs)



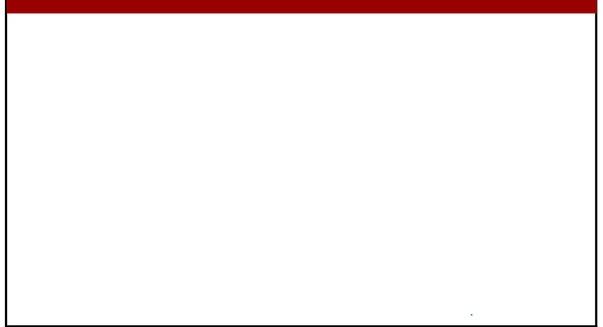
Grand average ERP (left) and CSD (right) waveform topographies for correct targets, nontargets, and novels

II. Midline CSD waveforms by group



Averaged midline CSD waveforms for patients and healthy controls for Novels (left column), Targets (center) and Nontargets (right). For Novels, a short latency sink (MMN) is followed by a source (Novelty P3) at central sites (CPz, Cz) and but is attenuated and delayed at anterior sites (peak latency approximates Target-P3).Vertical lines indicate peak latencies of CSD-PCA factors of interest (179, 241, 343; cf Fig. III)

IIIB. Temporal PCA Solution: Factor Score Topographies



Factor Score Topographies of first six factors. Correct Nontargets, Targets and Novels

Table 1 **Comparison of Varimax-rotated CSD-PCA initial components for Novelty with Dichotic and Binaural oddball tasks**

Novelty Oddball		Dichotic Oddball [1]		Binaural Oddball [2]		Interpretation [3]
Peak Latency [ms]	Explained Variance	Peak Latency [ms]	Explained Variance	Peak Latency [ms]	Explained Variance	
120	3.49	105	4.8%	105	4.5%	N1−
179	4.66	150	2.3%	160	3.9%	Temporal lobe N1−; MMN− for Novels
241	6.95	245	3.6%	215	5.3%	N2−; P3+ for Novels
343	17.49	440	30.3%	355	23.0%	P3+; P3+ for Novels
542	25.71	620	14.9%	560	24.0%	F−CP+
956	30.10	885	26.3%	920	25.6%	SW+ and noise variance

[1] Tenke et al. (2008)
[2] Kayser and Tenke (2006a)
[3] Identifying sink (−) and source (+) activity

Summary of Results

Comparable CSD-PCA factor structure for Novelty, Conventional and Dichotic oddballs tasks

- N1 (120 ms peak) sink/source topography is comparable for Targets, Nontargets and Novels, and consistent with activation of primary auditory cortex within the Sylvian fissure
- A subsequent sink (temporal N1; 179 ms) consistent with generators on the lateral surface of the temporal lobes, was observed for Targets, Nontargets and Novels
- Target-related P3 source (343 ms) is over parietal regions
- Target-related N2/P3 sequence (241 sink/ 343 source) evident

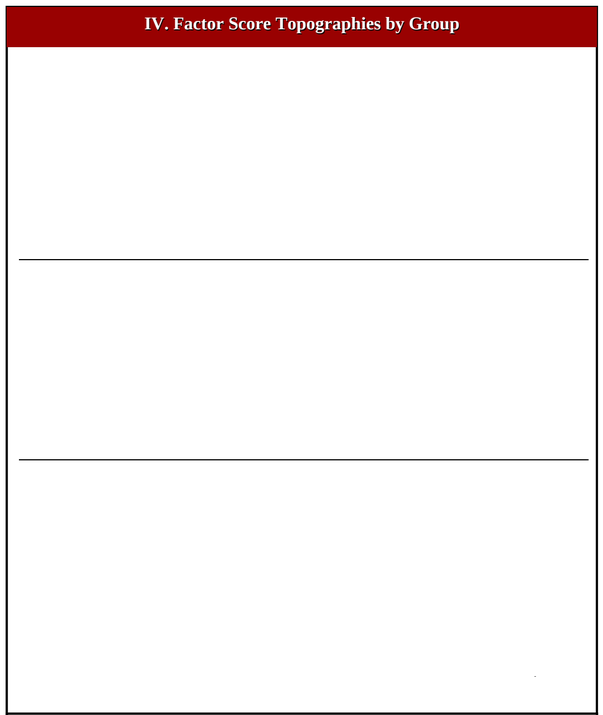
Unique to Novelty oddball task

- Frontal Target-N2 (241 ms) sink has a midline topography
- Target-P3 (343) source has secondary topography on frontal midline

Unique to Novel stimuli

- Central midline sink concurrent with temporal N1 (MMN sink; 179 ms)
- Early central midline source (Novelty P3 source; 241 ms)

IV. Factor Score Topographies by Group



Group differences in CSD-PCA factor score topographies. Patients show a marked reduction in early source activity (241 ms) at Cz to Novels (lower rows). This difference is not evident for the later P3 source (343), or for the preceding MMN sink (179).

ANOVA results for Novels (Fz, FCz, Cz, CPz)

	241	***341***
Group	[F(1,96)=5.52, p=.021]	
Group x Site	[F(3,288)=4.40; p=.014; epsilon=.664]	No Group effects
Simple effects highly significant *only* at Cz and CPz.		

(effect preserved with *age* or *performance* covariates)

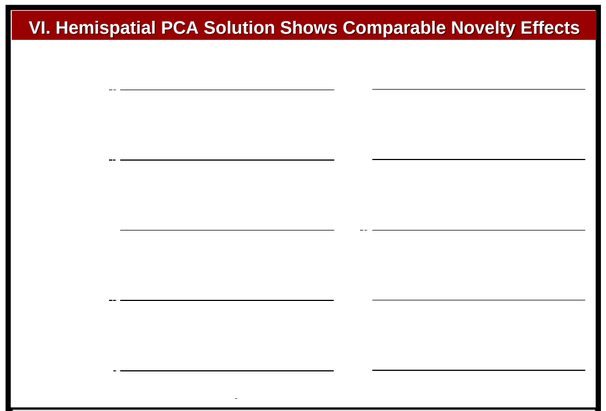
V. Reproducibility of Solution and Group Differences Across Blocks

PCA based on 4 conditions (Novels-1st half, Novels-2nd half, Nontargets, Targets) yielded comparable factors with similar differences in factor score topographies between groups.

Conclusions

- Novelty P3 source is reduced in Depressed Patients, but the reduction is **restricted** to the **earliest onset** of the P3 source (241 ms) at **central** sites
- The preceding MMN sink (179 ms) also has a midline central topography, but is preserved in patients
- The P3 source at **frontal** sites is: 1) **later** than at central sites; **2)** present for **both** novels and targets; 3) **preserved** in patients

VI. Hemispatial PCA Solution Shows Comparable Novelty Effects



Hemispatial factor loadings (maps) and factor score waveforms for Targets, Nontargets and Novels. *Left*. Factor score waveforms for the two hemispheres (identical colors) are closely comparable. Reference lines indicate peak latencies of the three factors of interest from the temporal CSD-PCA. *Right*. Averages across hemispheres for healthy controls (solid lines) and patients (dashed lines) for Targets, Nontargets and Novels support the identification of Group differences at Cz as the novelty P3 source, and distinct from a later target-related P3 source .

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